Abnormal Dark Adaptation and Rhodopsin Kinetics in Sorsby's Fundus Dystrophy

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Scotopic visual thresholds and time courses for dark adaptation were determined in eight patients with Sorsby's fundus dystrophy. Rhodopsin regeneration also was recorded in two. All patients had poor night vision and a visible yellow deposit at the level of Bruch's membrane that was confluent in the posterior pole. In retinal regions with the yellow deposit, scotopic thresholds were elevated, the rod-cone break was delayed or indistinct, the time courses for the rod portion of the dark adaptation curve was prolonged, and rhodopsin regeneration was slow in the one patient in whom measurements were made. In regions of ophthalmoscopically normal retina, dark adaptation was affected minimally, and in one patient, rhodopsin was regenerated at a normal rate. It was hypothesized that the abnormal dark adaptation and rhodopsin kinetics might be caused by reduced metabolic exchange across a thickened Bruch's membrane. Invest Ophthalmol Vis Sci 33:1633-1636, 1992

Sorsby's fundus dystrophy is characterized by autosomal dominant inheritance and loss of central vision after the fourth decade of life from either subretinal neovascularization or geographic atrophy of the outer retinal and inner choroid. Progressive peripheral chorioretinal atrophy may lead to a loss of ambulatory vision after the age of 70 years.1-5 Patients may be aware of difficulties in dark adaptation for a decade or more before losing central vision.5 Confluent yellow material at the level of Bruch's membrane is seen ophthalmoscopically, and it is believed to be the initial clinical manifestation of this disorder. It is seen initially at the posterior pole and slowly spreads into the peripheral retina. A diffuse deposit lying internal to the inner collagenous layer of Bruch’s membrane has been identified in an autopsy eye from a patient with Sorsby's fundus dystrophy.6 It is thickest in the posterior pole and is believed to be the histopathologic correlate of the yellow deposit seen clinically.

Psychophysical studies were done on eight eyes of eight patients with Sorsby's fundus dystrophy, poor night vision, and yellow Bruch's membrane deposits to quantify their visual deficits. In two patients, rhodopsin regeneration also was recorded.

Patients and Methods

All patients had 20/30 or better visual acuity in their studied eye and were 48–62 years of age. There were no ocular abnormalities, apart from the changes of Sorsby's fundus, and none had general disorders likely to cause visual loss, such as diabetes. None were receiving drugs known to affect vision.

For both the psychophysical and photochemical studies, the pupil was dilated with cyclopentolate 1%, and the patient was dark adapted for 45 min. Dark adaptation that was sufficient to bleach > 95% of the available rhodopsin was achieved with a calibrated indirect ophthalmoscope or with bleaching lamps installed in a modified Humphrey perimeter (Allergan Humphrey, Hertfordshire, England). The Tubinger7 or modified Humphrey automated perimeter was used to record dark-adaptation curves. For both perimeters, the stimulus was blue-green (wavelength, 500 nm [Tubinger] and 450 nm [Humphrey]) of 0.5-sec duration and Goldmann size V (102 min of arc in diameter). For each patient, dark-adaptation curves were measured in one or two additional locations; some locations corresponded with visible deposits, and others did not.

Rhodopsin regeneration was measured in two patients, using the imaging fundus reflectometer.9 The retina 25° temporal to fixation was bleached with a
white light (7.8 log scotopic troland-sec delivered over 45 sec), which is sufficient to bleach >95% of the available rhodopsin. At the retinal site measured, yellow material was seen in one patient but not in the other. Reflectometric measurements were obtained over the next 60 min as the patient was dark adapted. At the end of this period, another bleaching light was administered, and the measurements were repeated.

**Results**

Dark-adapted sensitivity losses ranging from 5–37 dB were recorded at locations subsequently selected for dark-adaptation curves (Table 1). A distinct rod-cone break could not be identified in many of the dark-adaptation curves. If none was evident, curve fitting was started after 30 min of dark adaptation. In all patients, there was a delay in the time course for the rod portion of the dark-adaptation curve with recovery of retinal sensitivity continuing up to 2 hr (Fig. 1). The delay in dark adaptation was more severe where the yellow deposit was identified (Table 1). This correlation existed for all eyes studied, but it was demonstrated best in eyes where the limits of the deposit were seen clearly ophthalmoscopically (Table 1, patients 2 and 4; Fig. 2).

Rhodopsin regeneration was normal in patient 2 (Table 1, Fig. 3) at a location where the dark-adaptation curve showed a small delay and which corresponded with a retinal locus where there was no visible yellow deposit (Fig. 2). Rhodopsin regeneration was delayed severely in patient 1 (Table 1, Fig. 3) at the same location where dark adaptation was prolonged (Fig. 1) and the yellow deposit was identified.

**Table 1.** Psychophysical and photochemical results in eight patients with Sorsby's fundus dystrophy

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>S</th>
<th>YD</th>
<th>Rod-cone break (min)</th>
<th>Rod</th>
<th>Rhodopsin regen.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>+</td>
<td>30</td>
<td>147.5</td>
<td>47.4</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>19</td>
<td>14.3</td>
<td>5.6</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>250.8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>+</td>
<td>—</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>97.8</td>
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</tr>
<tr>
<td>6</td>
<td>13</td>
<td>+</td>
<td>—</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>130.4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>—</td>
<td>—</td>
<td>12.3</td>
<td></td>
</tr>
</tbody>
</table>

Normal values: 10–12 min, 4–8 min

* In this patient, measurements could not be made beyond 40 min, and there was no distinct rod-cone break. For these reasons, a time constant for the rod portion could not be reliably determined.

S. scotopic threshold elevation, in decibels, prior to light adaptation. Patients 1–3 were measured with the Tubinger perimeter and the remainder with the modified Humphrey perimeter. YD, yellow deposit at retinal location measured (— = absent, + = present).

**Discussion**

The prolongation of dark adaptation appears to be a regional phenomenon occurring in areas in which yellow deposits were detected by ophthalmoscopy. In those areas in which deposits were not seen, the recovery from bleaching was normal or near normal. This deposit is believed to correspond to the continuous 30-μm thick amorphous material located between the retinal pigment epithelium cell basement membrane and the inner collagenous layer of Bruch's membrane. Although the precise effect of this deposit on the biophysical properties of Bruch's membrane is unknown, it has been suggested that it may act as a diffusion barrier, impeding metabolic exchange between the choroid and retinal pigment epithelium. It is well established that there is intense metabolic exchange across Bruch's membrane between the choriocapillaris and the retinal pigment epithelium and that photoreceptor function is dependent on this exchange. The profound functional loss probably is caused by deficient delivery to the photoreceptor cells of the metabolic substrates necessary for normal function. If the slightly prolonged time to the rod-cone break in areas in which the ocular fundus appeared normal is real, this may be related to the early effects on defective metabolic exchange because the abnormal layer in Bruch's membrane is found throughout the eye. It is seen in the posterior pole first only because it is thickest at this site rather than this being the only region affected.

The prolonged dark adaptation and reduced rate of rhodopsin regeneration seen in Sorsby's fundus dystrophy is similar to that seen in patients with severe vitamin A deficiency. Human and animal studies
suggest that, in vitamin A deficiency, recovery of retinal sensitivity is limited by the supply of chromophore rather than an intrinsic abnormality of the photoreceptor.\textsuperscript{11,12} Our findings in patient 1 showed that, when dark adaptation is delayed, rhodopsin regenerates at a reduced rate. Although it is difficult to compare the time constants for rhodopsin regeneration and sensitivity recovery precisely in the two patients in whom these measurements were made, there was a fairly good correlation between the timing of the rod-cone break and speed of rhodopsin regeneration. This suggests that the rates of both processes were affected similarly.\textsuperscript{11} The relative sparing of cone photoreceptor function compared with rod function seen in our patients is also a feature of vitamin A deficiency.\textsuperscript{11}

A diffusion barrier at the level of Bruch's membrane could account for the abnormal choroidal perfusion seen in this condition.\textsuperscript{5} If the anatomic and functional attributes of the choroidal capillaries are regulated by diffusible agents derived from the retinal pigment epithelium,\textsuperscript{13,14} metabolic isolation of one from the other may cause the choriocapillaris to revert to a more normal tubular system.\textsuperscript{16}

Patients with Sorsby's fundus dystrophy share many clinical and histopathologic features with those with age-related macular degeneration.\textsuperscript{17} Recent reports of poor choroidal filling\textsuperscript{18} and a loss of scotopic retinal sensitivity\textsuperscript{19,20} in patients with age-related macular degeneration suggest that the homology between the two disorders extends beyond simple anatomic findings. Our results imply functional impairment of the photoreceptor; this may be common to many disorders characterized by diffuse deposits within Bruch's membrane. Further studies of Sorsby's fundus dystrophy may yield results applicable to the more common disorder of age-related macular degeneration.

Key words: dark adaptation, imaging fundus reflectometry, rhodopsin kinetics, Sorsby's fundus dystrophy
References